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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/186,775	11/06/1998	DIANE BURGESS	012176-00621	2248

7590 08/20/2003

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EXAMINER	
HELMER, GEORGIA L	
ART UNIT	PAPER NUMBER
1638	29

DATE MAILED: 08/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/186,775	BURGESS ET AL.	
	Examiner	Art Unit	
	Georgia L. Helmer	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,2,4,6,7,11,14-16,18,20,21,25,26 and 28-37 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,2,4,6,7,11,14-16,18,20,21,25,26 and 28-37 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED OFFICE ACTION
09/186,775

Status of Claims

1. The request for a continued prosecution application (CPA) under 37 CFR 1.53(d) filed on 3 June 2003 is acknowledged. 37 CFR 1.53(d)(1) was amended to provide that the prior application of a CPA must be: (1) a utility or plant application that was filed under 35 U.S.C. 111(a) before May 29, 2000, (2) a design application, or (3) the national stage of an international application that was filed under 35 U.S.C. 363 before May 29, 2000. *See Changes to Application Examination and Provisional Application Practice*, interim rule, 65 *Fed. Reg.* 14865, 14872 (Mar. 20, 2000), 1233 *Off. Gaz. Pat. Office* 47, 52 (Apr. 11, 2000). Since a CPA of this application is not permitted under 37 CFR 1.53(d)(1), the improper request for a CPA is being treated as a request for continued examination of this application under 37 CFR 1.114. *See id.* at 14866, 1233 *Off. Gaz. Pat. Office* at 48.

2. Claims 1, 2, 4, 6, 7, 11, 12, 14-16, 18, 20, 21, 25, 26 and 28-37 are pending and are examined in the instant application. No claims have been amended.

Claim Rejections - 35 USC § 112 first paragraph

Enablement

3. Claims 1-2, 4, 6, 7, 11, 12, 14-16, 18, 20, 21, 25, 26, and 28-37 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record, as

set forth in the Office Action mailed March 1, 2002, and reiterated below. Applicant's arguments filed 3 June 2003 have been fully considered, but they are not persuasive.

Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)):

Nature of the invention. The claims are drawn to plant cells having at least two expression cassettes which when expressed in the same cell are lethal to the cell. And to methods of modifying plants which utilize plant cells having at least two expression cassettes which when expressed in the same cell are lethal to the cell. The claimed methods use site-specific recombination systems to modify gene expression.

State of the prior art. The state of the art is such that the skilled person can introduce a gene encoding a ribonuclease into a plant cell and express a single functional nuclease. However, the skilled person could not expect to express a single functional nuclease by introducing separate polynucleotides each encoding separate amino acid subsequences of a single functional ribonuclease. This is because many different subsequences of a nuclease could be used without ever getting the single functional nuclease. What is missing here is the idea that the polypeptide subsequences need to be complementary so that when used together in the same cell the whole functional nuclease is produced.

The art is such that the skilled person can introduce genes into plant cells but that generation of a given particular phenotype is unpredictable. Gene expression levels and inheritance are unpredictable (Deroles, SC and Gardner, RC; (1998) Plant Molecular Biology 11: 355-364 (X); Dunwell, JM and Paul, EM (1990) Outlook on

Agriculture 19, 103-109 (W); Finnegan J and McElroy D (1994) Bio/Technology 12: 883-888)(V). Organ-specific gene expression in plants is variable (Van-der-Hoeven C et. al. (1994) Transgenic Research 3: 159-166)(U). Recombinase mediated excision of appropriately flanked DNA sequences is variable and yields chimeric phenotypes having both recombined and unrecombined DNA (Gidoni, D. et al, Supplement to Plant Molecular Biology Reporter 18:2, S 03-40; ISPMB abstracts, June 18-24, 2000)(U). Recent studies (Gidoni, D et al (2001) Euphytica 121: 145-156)(U) of embryonal recombination and germline inheritance of recombined tobacco loci show variable recombination efficiencies (Godini 2001, 146 and 152). The claimed methods require use of site-specific recombination systems to delete appropriately flanked DNA sequences.

Breadth of the claims. Claims are broadly drawn to modifying cellular functions in a plant. There exist a large number of cellular functions which could be modified in a myriad of different ways resulting in potentially an infinite number of variations. Recombinases and recombinase sites are encompassed broadly.

Working examples. There are no working examples.

Guidance in the specification. The specification contains three prophetic examples: Prophetic Example 1 (p 20) describes the use of a repressor/activator fusion protein to induce expression of barnase in tapetal cells. Prophetic Example 2 (pg 21) describes use of the AVR9 elicitor polypeptide from *Cladosporium fulvum* and the corresponding resistance gene Cf19 from *Lycopersicon esculentum* to specifically kill tapetal cells. Prophetic Example 3 (pg 22) describes the use of cre-lox system to insert

two functional expression cassettes into a lox site previously introduced into a plant genome.

Prophetic Example 1 discloses sequences of steps for the use of the cre/lox system to create alternative alleles at one locus. At several points in these steps (page 20, Example 1), which are illustrated in Figure1, Applicant directs "Pick best" or "PCR". However Applicant gives no guidance on criteria or methods for picking the best or the meaning of "PCR." Applicant does not provide guidance for which of the various genes/promoters/cassettes in conjunction with recombinases and/or recombinase target sites can be successfully deployed to create male-sterile plants of otherwise modify cellular functions. See discussion above re the state of the prior art.

Applicant's 1.132 Declaration filed 2/13/01 (Exhibit 2) gives detailed information on the production of a functional nuclease when complementary subsequences of the nuclease polypeptide are expressed in the same cell. This data is from experiments using a CaMV 35S promoter, which is a constitutive promoter. The Declaration also includes (pg 4, Exhibit 1) information on use of a tapetum specific promoter to produce complementary subsequences of nuclease polypeptides in the same cell.

The Declaration has no information or data on the use of recombinases, recombination target sites, repressor/activator fusion proteins to induce expression of barnase in tapetal cells, use of the AVR9 elicitor polypeptide from *Cladosporium fulvum* and the corresponding resistance gene Cf19 from *Lycopersicon esculentum* to specifically kill tapetal cells, or the use of cre-lox system to insert two functional expression cassettes into a lox site previously introduced into a plant genome

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). Above discussions of predictability are repeated below:

The art is such that the skilled person can introduce genes into plant cells but that generation of a given particular phenotype is unpredictable. Gene expression levels and inheritance are unpredictable (Deroles, SC and Gardner, RC; (1998) Plant Molecular Biology 11: 355-364 ; Dunwell, JM and Paul, EM (1990) Outlook on Agriculture 19, 103-109 ; Finnegan J and McElroy D (1994) Bio/Technology 12: 883-888). Organ-specific gene expression in plants is variable (Van-der-Hoeven C et. al. (1994) Transgenic Research 3: 159-166). Recombinase mediated excision of appropriately flanked DNA sequences is variable and yields chimeric phenotypes having both recombined and unrecombined DNA (Gidoni, D. et al, Supplement to Plant Molecular Biology Reporter 18:2, S 03-40; ISPMB abstracts, June 18-24, 2000). Recent studies (Gidoni, D et al (2001) Euphytica 121: 145-156) of embryonal recombination and germline inheritance of recombined tobacco loci show variable recombination efficiencies (Godini 2001, 146 and 152).

Amount of Experimentation necessary. Applicant has provided no guidance on how to predictably eliminate inoperable embodiments from a virtually ad infinitum of possibilities other than by random trial and error, which is excessive experimentation and an undue burden.

Specifically, for any given set of transgenes in a plant, what phenotype is the desired one? For any given set of transgenes, criteria for parameters such as copy number, expression level (RNA or protein) of selectable marker, expression level (or

lack of expression) of genes of interest, expression patterns (or lack of expression) of genes of interest, and stability of transgenes through generations, need to be defined. In both of the prophetic examples for which Applicant includes schematic figures, four sets of transgenes need to be characterized and optimized for at least 5 sets of parameters to find the operable combinations. This represents 500+ combinations to be tested for this one embodiment, and represents excessive experimentation and an undue burden. The enablement of modifying all cellular functions would require an infinite number of variables to be defined and optimized.

In view of the breadth of the claims (modifying all cellular functions), the lack of guidance in the specification, and the unpredictability in the recombinase art, undue trial and error experimentations would be required to enable the invention as commensurate in scope with the claims.

Applicant traverses, stating primarily that one of ordinary skill in the relevant art, at the time of the filing of the...application, would have found the Applicant specification to sufficiently enable that person to achieve the system of the invention. That moreover, that person of ordinary skill would understand, by combining the teaching known in the art at the time with the teachings in Applicant's specification, how to achieve predictable and efficient impairing effects.

As evidence of this assertion, Applicant has submitted three references "which illustrate use of the cre/lox system to create predictable phenotypes".

Reference 1 is Dale et. al., 1991 (see attached 892 form).

Reference 2 is Qin et. al., 1994. (see attached 892 form).

Reference 3 is Odell et. al., US 5,658,772, issued August 1997 (see attached 892 form). (Response, p. 3)

Applicant traverses, stating primarily that Reference 1 teaches the introduction of a luciferase gene into the tobacco genome by using the hpt gene as a linked selectable marker. The hpt is flanked by recombination sites and is then excised from the plant genome by the Cre recombinase gene. (Response, p. 3)

Applicant's traversal has been considered and is unpersuasive because reference 1 characterizes segregation of the cre-nptII locus, using self pollination of two plants to produce R1 progeny and then looking at the various marker linkage in the R2 generation. One of the two plants demonstrated a segregation ratio of 7%, not the expected ratio of 25%, which was not further investigated (pages 1054 bridging to 1055). This evidences that this system is not "highly predictable and reliable nature of recombinase systems in general that is known to those of ordinary skill in this art".

Applicant traverses, stating primarily that Reference 2 teaches how to insert two different constructs into the tobacco genome, and states that progeny exhibit 67-100% co-transmission of the inserted transgenes, a percentage that indicates the highly predictable and reliable nature of

recombinase systems in general that is known to those of ordinary skill in this art. (Response, p3)

Applicant's traversal has been considered and is unpersuasive because Reference 2, (page 1709, Discussion) states that

> Based on the lack of site preference in T-DNA integrations and the 24 pairs of chromosomes in the N. tabacum genome, we have made the argument that the two lox sites are not likely to be on homologous chromosomes and even less likely to be within homologous regions. *Consistent with this contention, we found that the newly formed 35S-lox-hpt and lox-cre were cotransmitted (67-100%) to the same gamete* (emphasis added.). As homologous chromosomes segregate to different gametes, this high rate of cotransmission is consistent with the deduction that the two loci are most likely on nonhomologous chromosomes.

Applicant's recitation of the 67-100% cotransmission relates to whether transgenes segregated to the same or different gametes, and has no bearing on "the highly predictable and reliable nature of recombinase systems in general".

Applicant traverses, stating primarily that Reference 3 illustrated that prior to filing of the 5,658,772 patent, the use of site-specific recombinase of DNA was routine , predictable and efficient. And , "for example in '772, see Examples 12 and 13, which show use of the Cre/lox recombination system for the disruption of seed development. And also, Example 11, which illustrates the excision of a chimeric gene which causes male sterility for the purposes of restoring fertility". (Response, p. 3)

Applicant's traversal has been considered and is unpersuasive because Examples 11, 12 and 13 are prophetic examples and offer no data or other evidence of success of the recited embodiment.

Conclusion

4. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114, and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after filing of a request of a continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action

Remarks

5. No claims are allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Georgia L. Helmer whose telephone number is 703-308-7023. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 703-306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. All Technology Sector 1 fax machines are available to receive transmissions 24 hrs/day, 7 days/wk. Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

August 11, 2003
Georgia L. Helmer Ph.D.
Patent Examiner
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